

What is claimed is:

1. A chimeric polypeptide, said chimeric polypeptide comprising:

a) a first domain comprising extracellular or intracellular portions of a G protein coupled receptor, and

5 b) at least a second domain, attached to the first domain, wherein said second domain is naturally or non-naturally occurring hydrophobic moieties,

wherein said first domain does not comprise a native extracellular ligand of said GPCR.

10 2. The chimeric polypeptide of claim 1, wherein said second or more domains are attached at either one end, at both ends, or at an internal position of said first domain.

15 3. The chimeric polypeptide of claim 1, wherein said hydrophobic moiety is selected from the group consisting of: a lipid, an acyl or an amino acid.

4. The chimeric polypeptide of claim 3, wherein said hydrophobic moiety is selected from the group consisting of: palmitate (C16), myristoyl (C12), capryl (C10), caproyl (C6), phospholipids, steroids, sphingosines, ceramides, octyl-glycine, 2-cyclohexylalanine, or benzoylphenylalanine, wherein said hydrophobic moiety is
20 attached to said chimeric polypeptide with amide bonds, sulfhydryls, amines, alcohols, phenolic groups, or carbon-carbon bonds.

5. The chimeric polypeptide of claim 1, wherein said extracellular portion is selected from the group consisting of: the first extracellular domain or a fragment thereof, the second extracellular loop or a fragment thereof, the third extracellular loop or a fragment thereof, and the fourth extracellular loop or a fragment thereof, of said G-protein coupled receptor.

6. The chimeric polypeptide of claim 1, wherein said intracellular portion is selected from the group consisting of: the first intracellular loop or a fragment thereof, the second intracellular loop or a fragment thereof, the third intracellular loop or a fragment thereof, and the fourth intracellular domain or a fragment thereof, of said G-protein coupled receptor.

7. The chimeric polypeptide of claim 1 wherein said intracellular portion is selected from the group consisting of: an intracellular domain of a one-transmembrane domain G-protein coupled receptor of the cytokine GPCR, or a fragment thereof, or an intracellular domain of a multi-polypeptide-GPCR.

8. The chimeric polypeptide of claim 7, wherein said multi-polypeptide-GPCRs is selected from the group consisting of: a GPIIb/IIIa receptor or a collagen receptor.

9. The chimeric polypeptide of claim 5, wherein said extracellular portion of the GPCR is at least 3 contiguous amino acid residues.

10. The chimeric polypeptide of claim 6, where said intracellular portion is at least 3 contiguous amino acid residues.
11. The chimeric polypeptide of claim 6, wherein said intracellular portion is at least 5 contiguous amino acid residues.
12. The chimeric polypeptide of claim 6, wherein said intracellular portion comprises the third intracellular loop of the GPCR.
13. The chimeric polypeptide of claim 12, wherein said intracellular portion comprises at least 7 contiguous amino acid residues of the third intracellular loop.
14. The chimeric polypeptide of claim 1, wherein said second domain comprises a GPCR transmembrane domain or a fragment thereof.
15. The chimeric polypeptide of claim 14, wherein said transmembrane domain comprises at least 7 amino acid residues of TM5.
16. The chimeric polypeptide of claim 15, wherein said transmembrane domain comprises at least 14 amino acid residues of TM5.

17. The chimeric polypeptide of any one of claims 14, 15, or 16, wherein said amino acid residues are contiguous amino acid residues of TM5.

18. The nucleic acid of claim 1, wherein said G-protein coupled receptor is a mammalian G-protein coupled receptor.

19. The chimeric polypeptide of claim 18, wherein the G-protein coupled receptor or fragment thereof, is selected from the group consisting of a luteinizing hormone receptor, a follicle stimulating hormone receptor, a thyroid stimulating hormone receptor, a calcitonin receptor, a glucagon receptor, a glucagon-like peptide 1 receptor (GLP-1), a metabotropic glutamate receptor, a parathyroid hormone receptor, a vasoactive intestinal peptide receptor, a secretin receptor, a growth hormone releasing factor (GRF) receptor, protease-activated receptors (PARs), cholecystokinin receptors, somatostatin receptors, melanocortin receptors, ADP receptors, adenosine receptors, thromboxane receptors, platelet activating factor receptor, adrenergic receptors, 5-HT receptors, CXCR4, CCR5, chemokine receptors, neuropeptide receptors, opioid receptors, erythropoietin receptor, von Willebrand receptor, parathyroid hormone (PTH) receptor, vasoactive intestinal peptide (VIP) receptor, and collagen receptors.

20. The chimeric polypeptide of claim 1, wherein the hydrophobic moiety is a lipid.

21. The chimeric polypeptide of claim 20, wherein said lipid is a palmitate lipid.

22. A nucleic acid encoding the polypeptide of claim 1.

23. A recombinant vector comprising a nucleic acid of claim 22.

5

24. A host cell transformed with the recombinant vector of claim 23.

25. A method for producing a polypeptide of claim 1, comprising cultivating the host cell of claim 22 under conditions sufficient to express the receptor.

10

26. A method for identifying a potential therapeutic agent for use in treatment of a pathology, wherein the pathology is related to aberrant expression or aberrant physiological interactions of a GPCR, the method comprising:

15

(a) providing a cell having a GPCR or a property or function ascribable to said GPCR;

(b) contacting the cell with a composition comprising a candidate substance; and

(c) contacting the cell with a composition comprising the chimeric polypeptide of claim 1; and

20

(d) determining whether the composition comprising the candidate substance alters the property or function ascribable to said GPCR;

whereby, if an alteration observed in the presence of the substance is not observed when the cell is contacted with a composition devoid of the substance, the substance is identified as a potential therapeutic agent.

5 27. A method of treating or preventing a pathology associated with a GPCR, said method comprising administering the polypeptide of claim 1 to a subject in which such treatment or prevention is desired in an amount sufficient to treat or prevent said pathology in said subject.

10 28. The method of claim 27, wherein said subject is a human.

29. A pharmaceutical composition comprising the chimeric polypeptide of claim 1 and a pharmaceutically acceptable carrier.

15 30. A pharmaceutical composition comprising the nucleic acid molecule of claim 22 and a pharmaceutically acceptable carrier.

31. A kit comprising in one or more containers, the pharmaceutical composition of claim 29.

20

32. The use of a therapeutic in the manufacture of a medicament for treating a syndrome associated with a human disease, the disease selected from a pathology

associated with the polypeptide of claim 1, wherein said therapeutic is the polypeptide of claim 1.

33. A method for screening for a modulator of activity of a GPCR, said method comprising:

- a) administering a test compound to a first test animal, wherein said test animal expresses a desired GPCR;
- b) administering a polypeptide of claim 1 to a second test animal;
- c) measuring the activity of said test compound in said first test animal and said polypeptide in said second test animal; and
- c) comparing the activity of said polypeptide in said second test animal with the activity of said test compound in said first test animal with the activity of the desired GPCR in a control animal not administered said polypeptide,

wherein a change in the activity of said polypeptide in said first test animal relative to both said second test animal and said control animal indicates the test compound is a modulator of, an agonist of or an antagonist of said GPCR.

34. A method of treating a pathological state in a mammal, the method comprising administering to the mammal a polypeptide of claim 1.